REMARKS/ARGUMENTS

Applicants thank the Examiner for her time and consideration during the helpful telephonic interview of January 15, 2003.

Claims 40-48, 50, 112-119, 121 and 123 remain rejected in the pending application. New claim 124 is added herein, and support for the new claims is found in the specification on Page 24, Lines 10-14 and in original claim 45.

Issues under 35 U.S.C. §112, second paragraph

Claims 114 and 117 remain rejected under 35 U.S.C. §112, second paragraph in the pending application.

Claim 114 was rejected under 35 U.S.C. §112, second paragraph, for allegedly being indefinite regarding the term "vector" in the context of "liposome, protein, lipid, or carbohydrate". Applicants respectfully disagree, but in the interest of further prosecution of this matter have made an amendment to claim 114 without prejudice and without acquiescence. Applicants also submit herein new claim 124, directed to this matter.

Claim 117 was rejected under 35 U.S.C. §112, second paragraph, for allegedly being indefinite regarding the term "protein transduction domain." Applicants respectfully disagree. Applicants reiterate that the term is well-known in the art and therefore not indefinite. Although the Examiner states on page 3 of the Office Action, "However, HIV Tat is well known as comprising a "protein translocation domain," Applicants submit herewith the references of Ho *et al.* (2001), Morris *et al.* (2001), Ford *et al.* (2001), and Sherman *et al.* (2002) and refer the Examiner to the previously disclosed Schwarze *et al.* (1999), all of which clearly state that the domain is referred to as a "protein transduction domain." Thus, the term used by Applicants in the present invention is, in fact, well-known in the art and certainly definite. Furthermore, Applicants assert that they are not required to submit every example of a well-known term and are not indefinite for providing a single example. However, Applicants submit herewith Morris *et al.* (2001), Ford *et al.* (2001), and Sherman *et al.* (2002), citing other examples of protein transduction domains (which refer to VP22, the third α-helix of Antennapedia homeodomain, and HIV-1 Vpr), to illustrate the well-known and definite term in the art. Thus, Applicants respectfully request removal of this rejection.

Issues under 35 U.S.C. §112, first paragraph

Claims 40-48, 50, 112-119, 121 and 123 are rejected under 35 U.S.C. §112, first paragraph as allegedly not being written and described in a sufficient manner to show possession of the claims at the time of filing. Applicants respectfully disagree, but in the interest of furthering prosecution of this case Applicants submit claim amendments herewith without prejudice and without acquiescence. Specifically, Applicants remove the element "to about 20 contiguous residues" in the corresponding claims, as discussed with the Examiner in the telephonic interview. Applicants assert that the claims as amended certainly meet the requirements of written description under 35 U.S.C. §112, first paragraph and respectfully request removal of this rejection.

Claims 40-48, 50, 112-119, 121 and 123 are rejected under 35 U.S.C. §112, first paragraph as allegedly not being enabled for a skilled artisan to make and use the present invention. Applicants respectfully disagree, but in the interest of further prosecution of the present case Applicants submit herewith amended claims without prejudice and without acquiescence. Specifically, Applicants amend the claims to delivering "directly to an inner ear," as discussed with the Examiner in the telephonic interview. Applicants assert the specification and the knowledge of a skilled artisan are enabling to make and use the invention commensurate in scope with the amended claims. That is, Applicants assert that the specification and related art teaches delivering directly to an inner ear and also assert that it is unnecessary to limit the claims any further, as the Examiner suggests in the outstanding Office Action. Although direct injection into the inner ear is enabled for the present invention, a variety of references, submitted herewith, indicate methods other than injection are also known and used in the art for gene transfer into the ear (Staecker *et al.*, 1998; Jero *et al.*, 2001a; Jero *et al.*, 2001b; Stover *et al.*, 1999; Lalwani *et al.*, 1998) including providing a therapeutic effect (Staecker *et al.*, 1998). Therefore, a skilled artisan would know how to make and use gene transfer constructs *via* methods other than direct injection. For example, Staecker *et al.* (1998) describes gene therapy with brain derived neurotrophic factor preventing the degradation of auditory neurons wherein the gene was delivered through a microcatheter inserted into a cochleostomy in the inner ear. Jero *et al.* (2001a; 2001b) demonstrated gene transfer using adenovirus/liposome means applied to gelfoam, which permitted traversion of an intact round window membrane in the ear. Lalwani *et al.* (1998) describe gene transfer using an Alzet osmotic minipump delivered *via* cochleostomy.

Therefore, a variety of examples of gene delivery in the ear other than direct injection are known in the art.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendments. For the Examiner's convenience, Applicants are also attaching a set of currently pending claims.

Applicants believe no fee is due with this response other than a fee for Supplemental Information Disclosure Statement. Howe if a fee is due, please charge our Deposit Account No. 06-2375, under Order No. HO-P01899US2 from which the undersigned is authorized to draw.

Dated: Jan. 21, 2003

Respectfully submitted,

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Version With Markings to Show Changes Made

In the specification:

Please replace the paragraph beginning on Line 15 on Page 33 with the following paragraph:

In a specific embodiment, the present invention also provides a method of treating an animal in need of treatment for a deficiency in cerebellar granule neurons, a hearing impairment, an imbalance disorder, a joint disease, or in need of promoting mechanoreceptive cell growth, or a disease that is a result of loss of functional atonal-associated nucleic acid or amino acid sequences. This method comprises delivering a transcription factor having an amino acid with at least about 70% identity, preferably at least about 80% identity, and more preferably at least about 90% identity to the sequence AANARERRRMHGLNHAFDQLR (SEQ ID NO:70) to a cell in the animal. In some embodiments, the cell in the animal is located in the inner ear of the animal. Preferably, the transcription factor competes with atonal for binding to Daughterless protein (Jarman et al., 1993) or competes for binding with Math-1 to E47 protein (Akazawa et al., 1995).

In the claims:

Please cancel claim 50. Please add new claim 124.

40. (Amended Twice) A method of generating hair cells for an animal, comprising delivering directly to an inner ear a therapeutically effective amount of an atonal-associated nucleic acid sequence to a cell of said animal, wherein hair cells develop in said animal and wherein said atonal-associated nucleic acid sequence encodes a polypeptide that has hair cell generating activity and has at least about 80% identity to [about 20 contiguous residues of] SEQ ID NO:58.

48. (Amended Once) The method of claim 40, wherein said cell contains an alteration in an atonal-associated nucleic acid sequence [or amino acid sequence].

112. (Amended Twice) A composition comprising an *atonal*-associated nucleic acid sequence in combination with a delivery vehicle, wherein said delivery vehicle results in delivery of a therapeutically effective amount of *atonal*-associated nucleic acid sequence into a cell, and wherein said *atonal*-associated nucleic acid sequence encodes a polypeptide that has hair cell generating activity and has at least about 80% identity to [about 20 contiguous residues of] SEQ ID NO:58.

113. (Amended Once) The composition of claim 112, wherein said delivery vehicle comprises a vector that expresses an atonal-associated nucleic acid sequence [or amino acid sequence] in an animal cell.

114. (Amended Once) The composition of claim 113, wherein said vector is selected from the group consisting of a viral vector, a plasmid, [a liposome, a protein, a lipid, a carbohydrate and] or a combination thereof [of said vehicles].

121. (Amended Twice) A nucleic acid sequence encoding a fusion protein comprising an *atonal*-associated amino acid sequence or fragment thereof and a desired amino acid sequence, wherein said *atonal*-associated nucleic acid sequence encodes a polypeptide that has hair cell generating activity and has at least about 80% identity to [about 20 contiguous residues of] SEQ ID NO:58.

124. (New) The composition of claim 112, wherein said delivery vehicle is a liposome, a peptide, a lipid, a carbohydrate, or a combination thereof.